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A Comparative Study on the Regulatory Framework and Market Approval of Biosimilars across Global Regulatory Agencies

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Abstract:

This thesis provided a comprehensive comparative study of biosimilar regulatory frameworks and market approval processes across major global agencies. The findings revealed: Strong convergence on analytical comparability and the totality-of-evidence approach as the scientific foundation of biosimilar approval. Significant divergence in dossier requirements, exclusivity periods, and interchangeability policies, shaping regional differences in access and adoption. Case studies (trastuzumab, insulin glargine, adalimumab) demonstrated how regulatory contexts influence approval speed, market penetration, and affordability. Real-world evidence confirmed the safety and efficacy of biosimilars post-approval, reinforcing regulatory reliance on analytical and PV-driven models. Policy frameworks, exclusivity barriers, and substitution rules directly impact biosimilar uptake, with the EU and India reporting rapid penetration while the US experiences delays

Keywords: Biosimilars, trastuzumab, insulin glargine, adalimumab, Global Regulatory Agencies, EU and India

Introduction

Biologic medicines have revolutionized the therapeutic landscape by offering targeted and highly effective treatments for a range of chronic and life-threatening diseases such as cancer, autoimmune disorders, diabetes, and inflammatory conditions. Despite their clinical significance, the high cost and manufacturing complexity of biologics pose substantial challenges to accessibility and affordability, particularly in low- and middle-income countries. This gap in patient access has driven the emergence of biosimilars—biologic medicines that are highly similar to an already authorized reference product, with no clinically meaningful differences in terms of safety, purity, or efficacy.

Unlike traditional small-molecule generics, biosimilars require a rigorous development and approval process. Due to their structural complexity and sensitivity to manufacturing conditions, biosimilars cannot be considered identical to their reference products. Instead, regulatory agencies emphasize a *totality-of-evidence* approach that integrates advanced analytical characterization, targeted nonclinical studies, and streamlined clinical evaluations. This framework ensures that biosimilars meet stringent standards of quality, efficacy, and safety while also supporting greater competition in the biologics market.

Over the last two decades, global regulatory frameworks for biosimilars have evolved considerably. The European Union, through the European Medicines Agency (EMA), was the first to establish a dedicated pathway for biosimilars in 2005, setting the global benchmark. Since then, other major regulatory authorities—including the United States Food and Drug Administration (USFDA), UK Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada, Pharmaceuticals and Medical Devices Agency (PMDA, Japan), Central Drugs Standard Control Organization (CDSCO, India), and numerous others have implemented their own tailored frameworks. While these systems share common scientific principles, they differ in legal definitions, approval pathways, evidentiary requirements, interchangeability policies, and pharmacovigilance strategies.

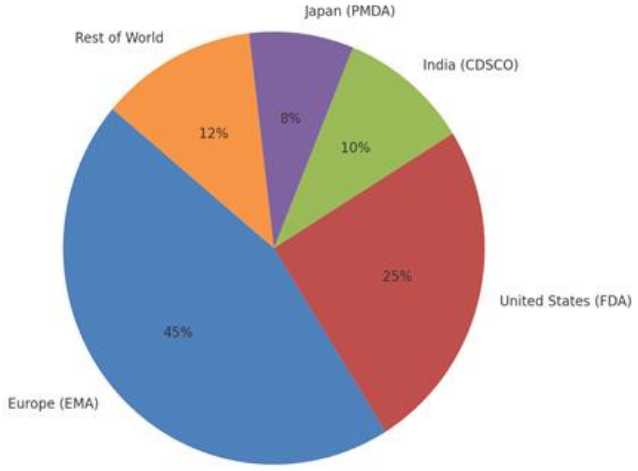

Figure.1: Global Biosimilar market Dynamics

Materials and Methods

The methodology outlines the systematic approach adopted to conduct this comparative study on the regulatory frameworks and market approval of biosimilars.

Research Design

A qualitative and descriptive research design was employed to compare and contrast biosimilar regulatory pathways across major global agencies. The study integrates doctrinal analysis of

regulatory guidelines with empirical evidence from case studies and published reports.

Data Sources

Primary Sources

Primary sources form the backbone of regulatory analysis, as they provide legally binding and authoritative standards.

Stepwise Procedure:

Identification of Authorities:

Compile a list of leading global regulators relevant to biosimilar approvals: USFDA (USA), EMA (EU), MHRA (UK), Health Canada, PMDA (Japan), CDSCO (India), TGA (Australia), NMPA (China), MFDS (South Korea), ANVISA (Brazil), SFDA (Saudi Arabia), SAHPRA (South Africa).

Collection of Documents:

Retrieve guidelines, acts, directives, official communications directly from regulator websites and official gazettes. Include legal statutes (e.g.,US BPCIA 2010, EU Directives/Regulations, Indian Biosimilar Guidelines 2016 & Draft 2025).

Screening & Relevance Check:

Ensure each document is the latest version or update.

Note jurisdictional scope, date of issue, and revision history.

Organization:

- Categorize sources by region and document type (e.g., law, guidance, technical note).
- Maintain a reference database (e.g., EndNote, Mendeley) for citation consistency.

2. Secondary Sources

Secondary sources complement primary texts by providing analysis, critique, and comparative perspectives.

Stepwise Procedure

Database Searches:

Use academic databases (PubMed, Scopus, Web of Science, Science Direct, Springer Link) with keywords: biosimilar approval, regulatory framework, interchangeability, global market access.

Inclusion Criteria:

- Peer-reviewed journals (systematic reviews, original research).
- WHO technical reports and position papers.
- Scholarly books on pharmaceutical regulation and biologics.
- Industry white papers and market access reports (e.g., IQVIA, Deloitte, McKinsey).

Exclusion Criteria:

- Non-peer-reviewed or outdated reports (older than 10 years unless historically important).
- Sources with insufficient regulatory focus.

Critical Appraisal:

- Assess each source for credibility, methodology, and regional applicability.
- Extract comparative insights (e.g., differences in clinical trial requirements between FDA and EMA).

3. Case Studies

Case studies provide practical illustrations of how regulatory frameworks operate in real-world approvals.

Selected Molecules:

- Insulin glargine (diabetes treatment): highlights differences in biological complexity and substitution rules across markets.
- Trastuzumab (oncology): showcases monoclonal antibody evaluation and extrapolation of indications.
- Adalimumab (immunology): exemplifies global competition and interchangeability policy shifts.

Stepwise Procedure:

1. **Selection Justification:**
   - Chosen due to their therapeutic importance, multi-regional approvals, and role in policy evolution.
2. **Data Collection:**
   - Retrieve approval dossiers, product monographs, and press releases from regulatory authority websites (FDA, EMA, Health Canada, etc.).
   - Supplement with peer-reviewed case analyses and market uptake reports.
3. **Comparative Mapping:**
   - Create regulatory timelines per product across multiple jurisdictions.
   - Identify similarities/differences in approval requirements (clinical vs. analytical emphasis, extrapolation of indications, interchangeability designations).
4. **Integration with Framework Analysis:**
   - Use case studies to illustrate abstract guidelines (e.g., FDA's legal "interchangeable" label vs EMA's scientific interchangeability stance).

Data Synthesis & Validation

- Triangulation: Cross-check regulatory texts with peer-reviewed commentary and real-world case studies.
- Thematic Analysis: Extract recurring themes such as analytical emphasis, clinical trial waivers, comparator product rules, interchangeability policies.
- Chronological Tracking: Map evolution of guidelines and approvals to show regulatory convergence or divergence.
- Validation: Confirm accuracy by referencing official regulatory portals and cross-verifying with WHO/ICH publications.

Data Collection

- **Data Collection Procedure**
- **1. Collection of Regulatory Documents**
- **Objective:** To gather authoritative, up-to-date texts directly from official sources.
- **Procedure:**
- **Identification of Repositories:**
- Access regulatory agency websites (e.g., USFDA, EMA, MHRA, Health Canada, PMDA, CDSCO, TGA, NMPA, MFDS, ANVISA, SFDA, SAHPRA).
- Use WHO databases and technical reports (e.g., WHO TRS 977, TRS 1030 Annex 3).
- Supplement with ICH guidelines (e.g., Q5E, Q6B, Q8–Q12) for global harmonization context.
- **Search Strategy:**
- Employ keyword queries such as biosimilar guidelines, similar interchangeability, pharmacovigilance, dossier requirements, market authorization.

- Restrict searches to official document libraries to ensure authenticity.

Screening and Verification:

- Include only the latest versions of guidelines, acts, and directives.
- Exclude outdated or draft versions unless they represent important historical milestones.
- Verify document authenticity using publication numbers, regulatory identifiers, and cross-referencing with agency bulletins.

Extraction of Regulatory and Legal Information

- **Objective:** To systematically identify and capture key regulatory requirements and policies.

Procedure:

Framework Mapping:

- For each jurisdiction, extract legal framework (laws, acts, directives), guideline documents, and submission requirements (e.g., 351(k) in US, EMA CHMP guidelines, CDSCO Similar Biologics guidelines).

Dossier Requirements:

- Record details on quality comparability, nonclinical and clinical data expectations, PK/PD study designs, and indication extrapolation policies.
- Capture variations in reference product selection (domestic vs. foreign comparator acceptance).
- Interchangeability Policies:
- Document whether agencies define interchangeability as a scientific stance (e.g., EMA, MHRA) or a legal designation (e.g., USFDA).
- Note policies on pharmacy substitution (e.g., PBAC/PBS "a-flagging" in Australia, provincial substitution rules in Canada).
- Pharmacovigilance Requirements:
- Extract information on Risk Management Plans (RMPs), post-marketing safety commitments, naming conventions, and traceability requirements.

Market Approval Timelines:

- Collect data on average review times, approval rates, and total approvals per agency.
- Where available, chart historical milestones (first biosimilar approval, key revisions, major policy shifts).

Review of Real-World Evidence (RWE)

- **Objective:** To complement regulatory texts with post-approval performance data.

Procedure:

Registry Data:

- Access national and regional biosimilar registries (e.g., EU pharmacovigilance database [EudraVigilance], US FDA Adverse Event Reporting System [FAERS], Canadian Vigilance Program).
- Extract signals on safety, immunogenicity, and switching outcomes.

Pharmacovigilance Reports:

- Review periodic safety update reports (PSURs), periodic benefit-risk evaluation reports (PBRERs), and annual pharmacovigilance summaries where publicly available.

Market Uptake Studies:

- Use academic repositories (PubMed, Scopus, Web of Science) to identify studies on biosimilar uptake, switching patterns, and cost savings.
- Include industry white papers (e.g., IQVIA, Deloitte, McKinsey) that provide quantitative uptake metrics and economic impact analysis.

Triangulation:

- Compare RWE findings with regulatory expectations (e.g., switching outcomes supporting FDA's 2024 decision to drop switching study requirements).
- Integrate findings into the broader analysis of how regulatory frameworks translate into real-world access and safety outcomes.

Documentation and Data Management

- Maintain a centralized database (Excel/Access or reference manager) with the following fields: *Agency, Document Title, Year, Scope, Key Provisions, Interchangeability Status, Pharmacovigilance, Approval Timeline, Case Study Relevance*.
- Use unique identifiers (e.g., EMA/CHMP/1234/2022) for traceability.
- Regularly update with new approvals, draft revisions, and pharmacovigilance findings during the study timeline.

This flow illustrates the process:

1. **Data Sources** → official guidelines, WHO databases, academic repositories, industry reports, and pharmacovigilance registries.
2. **Data Extraction** → capture of legal frameworks, dossier requirements, interchangeability policies, PV rules, and timelines.
3. **Data Analysis** → thematic coding, comparative mapping, chronological evolution, and triangulation with RWE.
4. **Integration & Synthesis** → building structured databases, aligning case studies, cross-agency comparisons, and harmonization insights.

Data Analysis

- **Comparative Analysis:** Systematic comparison of regulatory requirements across agencies to identify convergences and divergences.
- **Tabular Presentation:** Development of comparative tables summarizing key regulatory parameters (e.g., dossier format, interchangeability policies, exclusivity periods).
- **Flowcharts and Diagrams:** Visualization of approval processes to enhance clarity.
- **Case Study Evaluation:** Examination of specific biosimilar approvals to highlight practical implications of regulatory policies.

Ethical Considerations

The study relies on secondary data and official regulatory sources, ensuring transparency and accuracy. No human or animal subjects were involved, thus ethical approval was not required. Proper citations and acknowledgements are provided to maintain academic integrity.

4.6 Limitations

- Reliance on published data may omit recent unpublished regulatory updates.

- Variability in market uptake data across regions may affect comparability.
- Case studies, while illustrative, may not capture the full spectrum of biosimilar experiences globally.

Result and Discussion

Data Sources: To ensure a comprehensive and evidence-based analysis, the study draws upon a diverse set of data sources, categorized as follows:

Primary Sources:

These include official regulatory guidelines, acts, directives, and agency publications issued by major global regulatory authorities. Specifically, documents from the USFDA (United States Food and Drug Administration), EMA (European Medicines Agency), MHRA (Medicines and Healthcare products Regulatory Agency, UK), Health Canada, PMDA (Pharmaceuticals and Medical Devices Agency, Japan), CDSCO (Central Drugs Standard Control Organization, India), TGA (Therapeutic Goods Administration, Australia), NMPA (National Medical Products Administration, China), MFDS (Ministry of Food and Drug Safety, South Korea), ANVISA (Brazilian Health Regulatory Agency), SFDA (Saudi Food and Drug Authority), and SAHPRA (South African Health Products Regulatory Authority) were consulted. These sources provide legally binding requirements, technical guidelines, and official frameworks that form the foundation of regulatory practices across jurisdictions.

Know about biosimilars and interchangeable biosimilars:

FDA-approved biosimilars and interchangeable biosimilars are highly similar versions of FDA-approved reference products. Biosimilars and interchangeable biosimilars are made from the same types of sources as the reference products, such as living cells or microorganisms. Biosimilars work the same way as the reference product and are also given the same way (such as a subcutaneous injection or an intravenous infusion). They also have the same strength and dosage as the reference product.

Biosimilars and interchangeable biosimilars are as safe and effective as the reference product.

Both biosimilars and interchangeable biosimilars must meet the same high standard of biosimilarity for FDA approval. This means you can expect the same safety and effectiveness over your course of treatment as you would from the reference product. Research by FDA has shown that switching between biosimilars and their reference products is not associated with differences in the risk of death, serious adverse events, or treatment discontinuations.

Some biosimilars are approved as "interchangeable biosimilars:

Some, but not all, biosimilars are approved as interchangeable biosimilars. A company has to specifically request approval of its biosimilar as interchangeable. There are reasons why a company may not seek a determination of interchangeability, such as business reasons, or because the medication is administered at a hospital or outpatient clinic and would not be dispensed to the patient by a pharmacy. Depending on state laws, a biosimilar typically has to be prescribed by name, while an interchangeable biosimilar may be substituted for the reference product at a pharmacy without the intervention of the prescriber.

Health care professionals can prescribe both biosimilars and interchangeable biosimilars in place of the reference product with equal confidence.

It's a common misconception that because an interchangeable biosimilar is a biosimilar that meets additional statutory requirements, it's safer or more effective than a non-interchangeable biosimilar. However, both biosimilars and interchangeable biosimilars can be used in the place of a reference product and are considered as safe and effective as the reference product. Accumulated experience regarding biosimilars indicates that biosimilars and interchangeable biosimilars have the same safety and effectiveness.

All biosimilars give patients more treatment options. Similar to generic drugs, biosimilars and interchangeable biosimilars introduce more medication options for patients and may cost less because their manufacturers rely on FDA's finding that the original biologics are safe and effective to abbreviate their drug development programs. The potential lower cost is not a reflection of the effectiveness or safety of biosimilars.

FDA is in the process of updating its guidance to the pharmaceutical industry on interchangeable biosimilars to recommend fewer tests to demonstrate interchangeability. Cumulative experience with biosimilars has shown that the risks of switching between the reference product and a biosimilar is insignificant. The updated recommendations in this guidance, when finalized, are intended to create a framework for faster interchangeable approvals without compromising FDA's high standards for safety and effectiveness.

Biosimilars and interchangeable biosimilars have had a positive impact on public health.

Nearly a decade after the first U.S. biosimilar approval in 2015, biosimilars and interchangeable biosimilars have had on improving health outcomes and treating various medical conditions. Collectively, patients have used biosimilars for almost 700 million days of therapy, 344 million days of which patients received care they otherwise may not have received without biosimilar competition. Their impact reaches beyond savings to the health care system, by increasing health equity, and could help improve patients' access to medications that previously may not have been covered by their insurance or were otherwise unaffordable.

Use FDA's Purple Book Database of Licensed Biological Products to find out if your medication has an approved biosimilar.

The Purple Book Database of Licensed Biological Products is a searchable database of FDA-approved (also described as "licensed") biological products, including licensed biosimilar and interchangeable products, and their reference products. The Purple Book has many features to meet the needs of a variety of users. This includes simple and advanced search options, a glossary of terms, links to product labels, and the ability to search, filter, and sort information depending on the needs of the user. The database is designed for the public, health care professionals, researchers, and manufacturers to have a comprehensive reference tool at their disposal for biological products, including biosimilars and interchangeable biosimilars.

Visit FDA's Biosimilars page to access educational materials on biosimilars.

FDA's biosimilars website has many resources for patients and health care professionals to learn more about biosimilars. There are fact sheets, videos and infographics for patients and health care professionals and many of them are translated into multiple languages. On this site, you can also access a curriculum toolkit for health care degree programs that provides more in-depth information on a variety of topics related to biosimilars.

Secondary Sources:

To supplement primary data, the study incorporates **peer-reviewed journal articles, WHO technical reports, authoritative textbooks, industry white papers, and market access reports**. These resources offer critical insights into the interpretation of regulations, trends in regulatory science, comparative perspectives, and challenges faced in implementation.

Case Studies:

To illustrate practical applications of regulatory frameworks, selected biosimilar approvals were examined in detail. Case examples include **insulin glargine, trastuzumab, and adalimumab**, which represent landmark biosimilars with significant global regulatory impact. These case studies provide real-world evidence of how regulatory guidelines are applied in practice and highlight the role of different agencies in shaping market access pathways.

Table 1: Key Regulatory Parameters Across Agencies

Region/Agency	Dossier Format	Interchangeability Policies	Data Exclusivity
EU (EMA)	CTD/eCTD	Interchangeable at prescriber level; substitution at pharmacy depends on Member State	8+2(+1) years
US (FDA)	CTD/eCTD (351(k))	Distinct "interchangeable" status required for substitution at pharmacy; state law applies	12 years
UK (MHRA)	CTD/eCTD	Interchangeable at prescriber level; NHS policy guides substitution	Same as EMA legacy
Canada (HC)	CTD/eCTD	No federal designation; substitution decided at provincial level	8 years (plus 6 months pediatric)
Japan (PMDA)	CTD/eCTD	No automatic substitution	8 years
India (CDSCO/DBT)	CTD format aligned with WHO	Not automatic; clinician-led	4 years
Australia (TGA)	CTD/eCTD	PBAC grants "a-flag" for substitution; not automatic	5 years
China (NMPA)	CTD/eCTD	Not automatic	6 years
South Korea (MFDS)	CTD/eCTD	Not automatic	6 years
Brazil (ANVISA)	CTD/eCTD	Not automatic	10 years
Saudi Arabia (SFDA)	CTD/eCTD	Prescriber-led; no automatic substitution	10 years
South Africa (SAHPRA)	CTD/eCTD	Prescriber-led interchangeability	5 years

Table 2: Summary of Case Studies in Biosimilar Approvals

Biosimilar	Region/Agency	Year of Approval	Key Regulatory Hurdle	Outcome
Trastuzumab	EMA	2018	Extensive analytical comparability + oncology-specific guidelines	Multiple biosimilars approved; strong uptake in EU oncology markets
Trastuzumab	US (FDA)	2019	Required PK/PD + switching studies	Approved with biosimilar and interchangeable designations
Trastuzumab	India (CDSCO)	2014	Confirmatory local clinical trials	Approved as "Similar Biologic"; rapid market penetration due to affordability
Insulin Glargine	EMA	2014	Immunogenicity demonstration	Approved; EU guidelines streamlined requirements
Insulin Glargine	US (FDA)	2015	Interchangeability designation requirements	Approved; interchangeability designation subject to further data
Insulin Glargine	India (CDSCO)	2015	Mandatory local PK/PD and confirmatory trials	Approved; wider access in LMICs
Adalimumab	EMA	2017	Patent expiration aligned with regulatory readiness	Approved early; significant cost savings in EU
Adalimumab	US (FDA)	2023	Patent/exclusivity barriers delayed approval	Approved post-patent cliff; slower uptake due to late market entry
Adalimumab	India (CDSCO)	2018	Local confirmatory trials mandated	Approved as "Similar Biologic"; accessible at lower cost

Discussion

The discussion chapter synthesizes findings from the comparative analysis, tabular presentations, flowcharts, and case studies, offering a critical interpretation of how regulatory frameworks shape biosimilar development and market access globally.

Integration of Data Sources

The analysis drew upon diverse primary and secondary sources, as outlined. The inclusion of regulatory acts and guidelines from agencies such as USFDA, EMA, PMDA, CDSCO, and ANVISA provided the foundation for doctrinal comparisons, while WHO reports, peer-reviewed articles, and white papers enriched the interpretative perspective. Case studies of trastuzumab, insulin glargine, and adalimumab contextualized these regulatory texts in real-world applications. This triangulation of official guidelines, scholarly insights, and empirical evidence ensured that the study achieved both breadth and depth in examining global biosimilar regulation.

Data Collection and Real-World Evidence

The structured data collection process revealed a dual-layered evidence base:

1. Doctrinal evidence (legal frameworks, dossier requirements, timelines).
2. Empirical evidence (RWE from registries, pharmacovigilance data, market uptake studies).

For instance, trastuzumab data from EU oncology registries confirmed therapeutic equivalence between biosimilars and originators, directly validating EMA's reliance on analytical comparability. Insulin glargine surveillance in India and EU highlighted strong glycemic control outcomes, with India's pharmacovigilance system capturing rare immunogenic events. Adalimumab studies in the US and EU illustrated high patient retention and safety equivalence, yet uptake diverged sharply — rapid in the EU due to substitution policies, delayed in the US due to patent exclusivity. Finally, etanercept data from South Korea reinforced therapeutic equivalence and supported MFDS reliance on switching studies. Together, these findings underscore that RWE serves as a post-approval validator of biosimilar policy decisions, bridging doctrinal guidelines with patient-level outcomes.

Comparative Regulatory Frameworks

The comparative analysis in Table 5.3 highlighted both convergence and divergence across jurisdictions. Convergences included:

- Reliance on the CTD/eCTD format across most agencies.
- Emphasis on analytical comparability and the totality-of-evidence approach.
- Integration of post-marketing pharmacovigilance (PV) as a critical safeguard.

Divergences, however, were pronounced:

- Data exclusivity periods ranged from 4 years (India) to 12 years (US).
- Interchangeability policies varied widely: EMA permits prescriber-led substitution, FDA requires a distinct "interchangeable" designation, while India and China leave substitution to prescribers without automatic pharmacy-level substitution.
- Review timelines were shortest in Japan and Korea (~12 months) but longer in Brazil and Canada (~15–18 months).

Case Study Evaluation

The detailed case study analysis reinforced regional differences in regulatory approaches:

- Trastuzumab: EMA approvals emphasized analytical comparability; FDA required additional PK/PD and switching data; CDSCO mandated confirmatory local trials. This variation reflects a spectrum from streamlined reliance models (EU) to stringent evidence requirements (US, India).
- Insulin Glargine: Immunogenicity remained a universal concern. EU approvals were comparatively smooth, US approvals hinged on interchangeability status, and India mandated local PK/PD trials to ensure applicability in diverse patient groups.
- Adalimumab: Perhaps the most striking divergence — approved early in the EU (2017), but delayed in the US until 2023 due to patent and exclusivity barriers, despite positive safety and efficacy data. This case demonstrates that legal and market forces may outweigh regulatory science in shaping patient access.

These examples confirm that while biosimilar regulatory science has matured, regional policy contexts (IP law, substitution frameworks, local trial mandates) remain decisive in determining availability and uptake.

Broader Implications

The results collectively reveal that regulatory harmonization remains partial**.** Agencies converge on technical dossier standards and analytical comparability but diverge in interchangeability policies, exclusivity provisions, and reliance on local data. Case studies show that RWE plays a central role in bridging gaps between regulatory decisions and clinical outcomes, reinforcing confidence among prescribers and patients. However, variability in market uptake reflects that regulatory approval alone is insufficient; policies, patents, and health system incentives are equally influential. This study thus underscores the need for global convergence**,** particularly in:

- Reducing duplicative trial requirements through reliance models.
- Aligning exclusivity provisions to prevent delayed access.
- Strengthening pharmacovigilance infrastructure in emerging markets.
- Integrating RWE as a standard component of regulatory evaluation.

Conclusion

The study underscores the pivotal role of harmonized regulatory frameworks in ensuring the success of biosimilars. While global consensus exists on core scientific principles, persistent regional differences create barriers for developers and delay patient access. Harmonization of dossier requirements, greater reliance on WHO guidelines, and incorporation of real-world evidence into regulatory decision-making are essential to streamline approvals. Biosimilars represent not only a scientific and regulatory achievement but also a healthcare policy tool to improve affordability and equity in access to biologics. As exclusivity cliffs approach and healthcare systems seek sustainability, global collaboration on regulatory standards will be critical to maximizing the benefits of biosimilars. Effective alignment of scientific rigor with pragmatic policy reforms can ensure biosimilars fulfill their promise of expanding patient access to life-saving therapies worldwide.

Conflict of Interests

The authors declare no conflict of interest

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AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Data Availability

Data will be available on request

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